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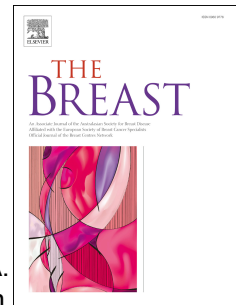
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Accepted Manuscript

The presentation, management and outcome of inflammatory breast cancer cases in the UK: Data from a multi-centre retrospective review

E. Copson, A.M. Shaaban, T. Maishman, P.M. Moseley, H. McKenzie, J. Bradbury, A. Borley, M. Brzezinska, S.Y.T. Chan, J. Ching, R.I. Cutress, I. Danial, B. Dall, M. Kerin, A.J. Lowery, I.R. Macpherson, L. Romics, E. Sawyer, N. Sharmat, T. Sircar, R. Vidya, Y. Pan, D. Rea, L. Jones, D.M. Eccles, F. Berditchevski



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The presentation, management and outcome of inflammatory breast cancer cases in the UK: data from a multi-centre retrospective review

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Running title: Inflammatory breast cancer: the UK experience

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Abstract

Objectives

Inflammatory Breast cancer (IBC) is a rare but aggressive form of breast cancer. Its incidence and behaviour in the UK is poorly characterised. We collected retrospective data from hospitals in the UK and Ireland to describe the presentation, pathology, treatment and clinical course of IBC in the UK.

Materials and Methods

Patients with IBC diagnosed between 1997 -2014 at fourteen UK and Irish hospitals were identified from local breast unit databases. Patient characteristics, tumour pathology and stage, and details of surgical, systemic and radiotherapy treatment and follow-up data were collected from electronic patient records and medical notes.

Results

This retrospective review identified 445 patients with IBC accounting for 0.4-1.8% of invasive breast cancer cases. Median follow-up was 4.2 years. 53.2% of tumours were grade 3, 56.2% were oestrogen receptor positive, 31.3% were HER2 positive and 25.1% were triple negative. 20.7% of patients had distant metastases at presentation. Despite trimodality treatment in 86.4%, 40.1% of stage III patients developed distant metastases. Five-year overall survival (OS) was 61.0% for stage III and 21.4% for stage IV patients.

Conclusions

This is the largest series of UK IBC patients reported to date. It indicates a lower incidence than in American series, but confirms that IBC has a high risk of recurrence with poor survival despite contemporary multi- modality therapy. A national strategy is required to facilitate translational research into this aggressive disease.

Key words: Inflammatory breast cancer, Breast, Cancer, Large cohort

Introduction

First described in 1924, inflammatory breast cancer (IBC) is a rare but aggressive form of invasive breast cancer [1]. US registry data indicate that IBC accounts for 2-4% of breast cancer cases but up to 10% of breast cancer deaths owing to the associated poor prognosis [2,3]. In other industrialised countries the incidence of IBC varies from 0.09-2.9% (Japan) to 0.6-2.0% (Italy) [4,5]. No comparable data are available for the UK, as IBC cases are not identified within National Cancer Intelligence reports [6].

The diagnosis of IBC is based on clinical features of erythema and skin oedema with prominent dermal hair follicles (peau d'orange) of less than 6 months duration [7,8], and no unique histological identifiers [9]. Dermal lymphatic invasion (DLI) with tumour emboli is considered a histological hallmark, being the primary cause of the breast lymphatic obstruction seen in IBC, but is identified in less than 75% of IBC cases [10].

Clinical guidelines recommend use of aggressive primary systemic therapies; however outcomes remain poor with series reporting high rates of systemic recurrence and poor overall survival [9, 11, 12]. A better understanding of the biology of IBC is clearly required [3], but clinical trial data for interventions in IBC are severely limited. A 2011 multidisciplinary meeting of UK specialists with an interest in IBC resulted in the establishment of the UK IBC consortium, [13]. Our aims are to establish a national mechanism for conducting research into IBC, through provision of practical guidelines to encourage: 1) consistent definition, 2) uniform collection of diagnostic information, and 3) standardisation of treatment approaches. To inform the design of future prospective and interventional studies, we have reviewed the incidence, pathology, treatment and outcomes of UK IBC patients with primary IBC (IBC in a previously normal breast) treated at thirteen UK and one Irish breast cancer units between 1997 and 2014.

Patients and Methods

Breast unit databases at fourteen participating hospitals were reviewed to identify patients with primary invasive breast cancer documented as IBC and /or TNM stage T4d and diagnosed between 2014 and 1997 (or as far back as records were available). Participating centres were chosen to represent different geographical regions: 3 centres from central England; two from London; three from the South; one from North England; two from Scotland; one from Wales; one from Ireland. Medical records were interrogated to confirm that identified cases fulfilled clinical criteria for a diagnosis of IBC published at the time of presentation [7-9]. Patients received treatment and follow-up according to local protocols. The total number of breast cancer cases diagnosed at each unit during the record availability period was requested. Data were collected from hospital electronic patient records and patient case notes. Patient characteristics, imaging findings, tumour pathology, disease stage, and treatment received pathological response rate, time to loco-regional and distant disease recurrence, site of metastases, and overall survival were recorded. Follow-up data were censored at last clinic attendance. Hormone receptor levels equivalent to an Allred score of >2 were categorised as positive [14]. A complete pathological response after primary chemotherapy was defined as no residual invasive carcinoma within the breast (DCIS permitted) following surgery and no evidence of metastatic disease within resected lymph nodes. A partial response was defined as showing residual disease following surgery with some features of response to therapy [15].

All data collections were registered and approved locally. Storage and transfer of anonymized data were performed according to institutional governance protocols.

Statistical Analyses

Summary statistics were used to describe both cohorts. Analyses were performed in STATA v11.2. Overall survival (OS) and distant relapse free survival (DRFS) were assessed using Kaplan-Meier curves and their corresponding hazard rates were evaluated using Cox proportional hazards model. OS and DRFS were assessed as time from date of invasive breast cancer diagnosis to death from any cause (OS), and to date of distant relapse or death from breast cancer (DRFS). Patients

who had not experienced an event at the time of analysis were censored at their date of last follow-up. Patients with Stages III and IV at presentation were analysed separately for OS.

Results

A total of 445 patients with IBC diagnosed between 1997-2014 were identified by the 14 participating hospitals. Ten breast cancer units provided numbers of total invasive breast cancer cases diagnosed during the search period; the incidence of IBC at these units ranged from 0.4% - 1.8%. Full details of the hospitals involved and number of cases submitted are provided in Supplementary Table 1.

Patient Characteristics

Table 1 demonstrates patient demographics. Median age at diagnosis of IBC was 56 years, (range 26-92). Data on ethnicity were available for 248 patients: 88.7% of these were white/Caucasian. Body mass index data were available for 160 patients (36%); median BMI at presentation was 28.72 kg/m² (range 18.2-48.9) with 26.3% within the World Health Organisation healthy weight category (BMI 18.5-24.9 kg/m²), 31.9% being overweight (BMI 25.0-29.9 kg/m²) and 41.3% being obese (BMI ≥ 30.0 kg/m²).

Presentation and Diagnostics

Patient presentation details were provided for 226 cases and 19% (43) of these were treated for presumed infection prior to diagnosis of IBC. Sonographic results were available for 314 cases (Table 1). Four patients had bilateral tumours. A measurable tumour mass was visible on initial imaging in 276 cases (87.9%) with a median size of 40 mm (range 5.4-145), whilst diffuse changes only were visible in 38 (12.1%). One hundred and forty-two tumours were multifocal (40.5%) and oedema was present in 250 (82.8%). All patients had a core biopsy. Skin punch biopsies were performed in 18 cases: 13 (72.2%) were positive for malignant cells. Abnormal axillary lymph nodes were seen on imaging in 301 cases (86.7%). Data on core biopsy and/or fine needle

aspiration of axillary lymph nodes were available for 252 cases, and 214 of these (84.9%) were positive for malignant cells. Evidence of distant metastases at presentation was found in 20.7% of patients (90/434).

Patient demographics	Number (n=445)	Percentage	Imaging	Number (n=449 [#])	Percentage
Year of Diagnosis			Sonographic appearance		
1990-2000	9	2	Measurable tumour mass	276	87.9
2001-2005	41	9.2	Diffuse changes only	38	12.1
2006-2010	204	45.8	Missing	135	30.1
2011-2015	191	42.9	Multifocal disease		
Missing	0	0	Yes	142	40.5
Age / years			No	209	59.5
Median (range)	56 (26--92)		Missing	98	21.8
Ethnicity			Diameter of tumour mass/mm		
White/ Caucasian	220	88.7	Median, (range)	40 (5.4-145)	
Asian	13	5.2	Missing	135	
Black	12	4.8	Oedema		
Other	3	1.2	Yes	250	82.8
Missing	197	44.3	No	52	17.2
Treatment of Stage III patients	Number (n=344)	Percentage	Missing	147	32.7
Systemic therapy			Abnormal axillary LN		
Neoadjuvant chemo	323	94.2	Yes	301	86.7
Neoadjuvant endocrine	9	2.6	No	46	13.3
Adjuvant chemotherapy	3	0.9	Missing	102	22.7
No systemic therapy	8	2.3		n=445	percent
Missing	1	0.3	Distant metastases		
Chemotherapy regimen			Yes	90	20.7
Anthracycline / Taxane	199	62	No	344	79.3
Anthracycline/ no	107	33.3	Missing	11	2.5
Taxane/ no anthracycline	12	3.7	Tumour Pathology	Number (n=449 [#])	Percentage
Other	3	0.9	Histological Type		
Missing	5	1.5	Ductal carcinoma	371	84.3
Trastuzumab (HER2+pts)			Lobular carcinoma	45	10.2
Yes	86	86	Mixed ductal/lobular	6	1.4
No	14	14	Other	18	4.1
Breast Surgery			Missing	9	2
Mastectomy	288	85.7	Grade		
Skin sparing	5	1.5	1	20	4.8
Breast conserving	20	6	2	176	42
BCS with subsequent	3	0.9	3	223	53.2
No surgery	20	6	missing	30	6.7
Missing	8	2.3	Tumour Diameter*		
Axillary Surgery			Median (range)	24 (0--	
Axillary node clearance	175	78.5	Missing/unavailable	120	
Sentinel node biopsy	15	6.7	ER status		
SNB followed by ANC	6	2.7	Pos	248	56.2
Axillary sampling	7	3.1	Neg	193	43.8
No axillary surgery	20	9	Missing	8	1.8
Missing	121	35.2	PR status		
Radiotherapy			Pos	128	38.2
Breast (BCS patients, n=20)			Neg	207	61.8
Yes	17	100	Missing	114	25.4
No	0		HER2 status		
Missing	3	15	Pos	133	31.1
Chest wall (mastectomy)			Neg	295	68.9
Yes	255	93.8	Missing	21	4.7
No	17	6.3	ER/PR/HER2 status		
Missing	16	5.6	Triple negative**	107	25.1
Axilla			Not triple negative	320	74.9
Yes	41	15.4	Missing	22	4.9
No	226	84.6	Lymphovascular Invasion		
Missing	77	22.4	Yes	129	39.8
Supraclavicular Fossa			No	195	60.2
Yes	153	52.2	Missing	125	27.8
No	140	47.8	Nodal status*		
Missing	51	14.8	Pos	128	35.1
			Neg	237	64.9
			Missing	84	18.7

[#]Includes 4 patients with bilateral tumours

*post neo-adjuvant chemotherapy in 327 cases** ER/PR and HER 2 negative or ER/HER2 negative and PR unknown

Table 1: Patient characteristics, imaging results, tumour pathology and treatment
Tumour Pathology

Tumour core pathology details are presented in Table 1. Grade 3 tumours represented 53.2% of all cases, 56.2% were oestrogen receptor (ER) positive, and 31.1% were HER2 positive, with 25.1% having triple negative phenotype (ER and HER2 negative, with PR negative or unknown). Vascular invasion was identified in 39.8% of tumours.

Treatment of non-metastatic patients

Systemic therapy and response

Treatment received by confirmed stage 3 patients (n=344) is summarised in Table 1. Primary chemotherapy was used in 94.2% of patients, with 0.9% receiving adjuvant chemotherapy. Most patients received anthracycline/taxane combination chemotherapy (62.0%) or another anthracycline based regimen (33.3%). Eighty- six per cent of HER2 positive patients received neo/adjuvant trastuzumab. Three patients received bevacizumab. A complete pathological response (pCR) was recorded in 18.1% of patients treated with primary chemotherapy (Table 2), with pCR rates in different biological subtypes varying as follows: ER positive/ HER2 negative (ER+HER2-) 9.8%; ER positive/HER2 positive (ER+HER2+) 18.9%; ER negative/ HER2 positive (ER-HER2+) 34.7%; ER negative/HER2 negative (ER-HER2-) 18.8% (Table 2). Taxane chemotherapy was associated with a pCR rate of 19.6% compared to 13.3% for non-taxane regimes (p=0.019). In HER2 positive patients, the pCR rate was 27.5% in patients who received trastuzumab compared to 14.3% in those who did not (p=0.669). No response data were available for the 9 patients treated with neoadjuvant hormonal therapy.

Surgical Treatment

Surgery was performed in 94% of stage 3 patients, with 86.6% undergoing mastectomy (as primary or secondary procedure), 1.5% having a skin-sparing mastectomy and 6.0% having breast conserving surgery. Axillary node clearance was performed in 81.2% of patients; 35.1% had positive nodal involvement at pathological review.

Biological Subgroup	All N=344	ER + HER2 – N=143	ER + HER2 + N=43	ER – HER2 + N=56	ER- HER2 – N=91	p-value (Fishers-Exact)
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Pathological response No. assessable	323*		122		37		49		85		ER-HER2- vs other groups P=0.7392
CR	55	18.2	12	9.8	7	18.9	17	34.7	16	18.8	
PR	185	61.1	80	65.6	26	70.3	28	57.1	44	51.8	
NR/PD	63	20.8	30	24.6	4	10.8	4	8.2	25	29.4	
missing	20	6.2	9	6.9	3	7.5	7	12.5	4	4.5	
Distant metastases											ER-HER2- vs other groups P=0.0016
Yes	136	40.1	52	37.1	11	26.8	18	40.0	50	55.6	
No	203	59.9	88	62.9	30	73.2	27	60.0	40	44.4	
Missing	5	1.5	3	2.1	2	4.7	1	2.2	1	1.1	
5 yr DRFS % (95% C.I.)	55.2 (48.8-61.1)		63.1 (53.1-71.5)		54.8 (30.2-73.9)		57.4 (40.0-71.4)		38.6 (27.2-49.7)		
HR			1.23 (0.64, 2.35)		1.0 (ref cat)		1.30 (0.61-2.75)		2.28 (1.18,4.39)		
p-value			0.541				0.492		0.014		
5 yr OS % (95% C.I.)	61.0 % (54.8-66.6)		70.0 (60.3-77.7)		76.9 (56.6-88.6)		66.2 (49.8-78.3)		37.7 (26.6-48.8)		
HR			1.47 (0.69-3.13)		1.0 (ref.cat)		1.60 (0.69-3.71)		3.22 (1.53-6.80)		
			0.3515				0.273		0.002		

*Excludes patients who did not receive neoadjuvant chemotherapy, undergo surgery and have available data on pathological response

Table 2: Pathological response rates, distant recurrence rates, DRFS and OS of stage 3 patients in retrospective review; whole cohort and biological subgroups classified by ER and HER2 status

Radiotherapy

All patients treated with breast conserving surgery received breast irradiation, and 93.8% of mastectomy patients received radiotherapy to the chest wall. Irradiation of the ipsilateral axilla and/or supraclavicular fossa was performed in 15.4% and 52.2% of patients, respectively.

Data regarding all three treatment modalities (chemotherapy, surgery and radiotherapy) were available for 316 patients: 86.4% received trimodality treatment.

Treatment of patients with stage IV disease at presentation

Data regarding systemic treatment were available for 88 of the 90 patients with evidence of distant metastases at presentation: 79.5% (70/88) received chemotherapy (26 had anthracycline based chemotherapy; 34 anthracycline/ taxane combination chemotherapy; 5 had taxanes only; 1 had a non-anthracycline/ taxane chemotherapy), 6.8% (6/88) received hormonal therapy but not

chemotherapy and 13.6% (12/88) received no systemic treatment. Fifty-five point three per cent of the metastatic patients underwent surgery (44/85 had mastectomy and 3/85 had breast conserving surgery); no surgery was performed in 44.7% of cases. Radiotherapy to the breast or chest wall was performed in 52.4% of metastatic cases (43/82).

Follow-up and Survival

Median follow-up was 4.2 years (range 0.2 to 18.2 years). A total of 186 deaths were recorded; cause of death was available for 122 patients of whom 109 (89%) died of metastatic breast cancer. Median overall survival (OS) was 7.5 years for patients with stage 3 disease at diagnosis, and 1.9 years for stage 4 disease, with 5-year OS rates of 61.0% and 21.4% respectively (figure 1a). Of 344 patients with confirmed stage 3 disease at presentation, 136 (40.1%) subsequently developed distant metastases with a 5-year DRFS of 55.2% (figure 1b). The most frequent sites of first recurrence were liver (40.8%), lung (34.4%), bone (30.4%), brain (23.2%), subcutaneous tissue (15.2) and mediastinum (12.8%) with some patients having first recurrence at more than one site. Higher rates of CNS recurrence were seen in the ER+HER2+ (27.3%), ER-HER2+ (33.3%), and ER- HER2- (20.8%) patients, compared to ER+HER2- (14.9%) cases. Data on locoregional recurrence (LLR) post-surgery were available for 237 patients with 50 events reported (21.1%); 44 LRRs occurred in patients having mastectomies (20.7%), 3 in WLE patients (14.2%), 2 in WLEs with completion mastectomies (66.7%) and 1 in a skin sparing mastectomy case (20%).

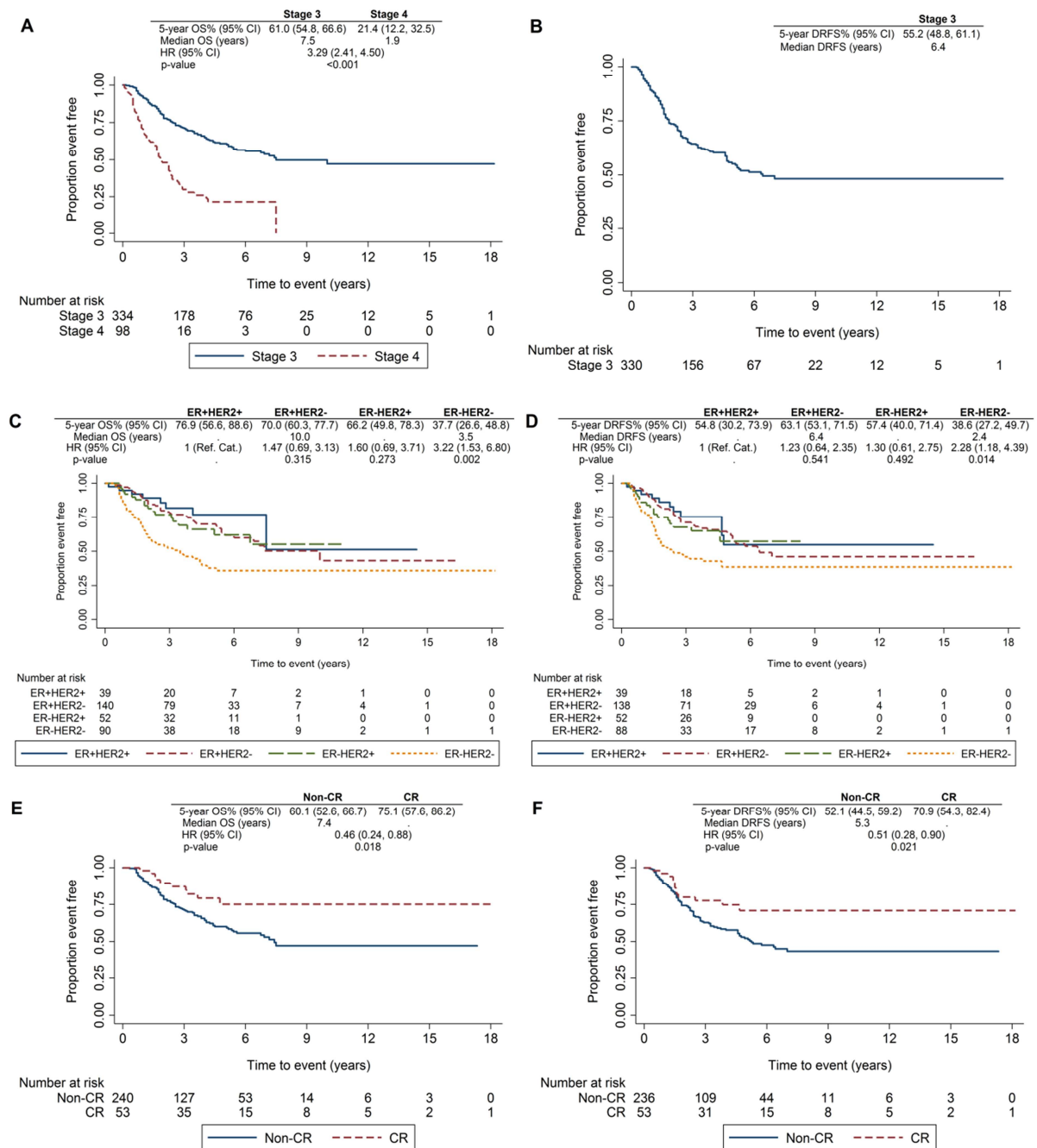


Figure 1: Kaplan-Meier curves illustrating a) overall survival (OS) in stage III and stage IV patients; b) distant recurrent free survival (DRFS; stage III patients only); c) OS and d) DRFS in stage III patients categorised by ER and HER2 status; e) OS and DRFS and f) in stage III patients categorised by complete pathological response and non-complete pathological response to primary chemotherapy.

When stratified by age, OS (but not DRFS) rate was higher in younger patients (i.e. < 50 y.o.) ($p=0.01$, Table 3). Five-year OS and DRFS were significantly poorer in ER-HER2- and triple-negative patients, compared to the other biological subtypes (37.7% OS and 38.6% DRFS vs 76.9% OS and 54.8% DRFS for ER+HER2+; 70.0% OS, 63.1% DRFS for ER+HER2- and 66.2% OS and 57.4% DRFS for ER-HER2+; OS $p<0.002$ and DRFS $p<0.014$) (Figure 1 c/d). Pathological complete response (pCR), following primary chemotherapy, was associated with a significantly greater 5-year OS, compared to those who only achieved a partial response or stable disease (75.1% vs 60.1%, $p=0.018$) (figure 1e). Nodal involvement and vascular invasion (LVI) were also associated with poorer DRFS and OS (Table 3). Cox regression multivariate analysis demonstrated that age, triple negativity and LVI remained significant independent factors for OS (Table 4).

Thirty two invasive lobular cancers (ILC) patients were identified in our cohort (~9.4%). Responses to chemotherapy in these patients were similar to those observed in the IDC group ($p=1.0$ in Fisher's exact test). Although not statistically significant, we noted a trend suggesting that lobular histology was associated with a worse outcome than ductal histology (HR, 1.58; 95% CI, 0.97-2.59, $p=0.069$).

	OS			DRFS		
	Hazard Ratio	95% Confidence Interval	P value	Hazard Ratio	95% Confidence Interval	P value
Age, years						
Age < 50	1.00 (Reference)			1.00 (Reference)		
Age >= 50	1.73	(1.14-2.63)	0.010	1.13	(0.78-1.63)	0.507
Grade						
Grade 1	1.00			1.00		
Grade 2	1.15	(0.49-2.67)	0.749	0.98	(0.44-2.14)	0.950
Grade 3	1.14	(0.49-2.63)	0.768	1.05	(0.48-2.30)	0.896
Multifocal disease						
No	1.00			1.00		
Yes	1.08	(0.69-1.66)	0.744	1.13	(0.74-1.74)	0.574
Pathological response						
CR	1.00			1.00		
NR	3.93	(1.94-7.95)	0.000	3.53	(1.87-6.65)	0.000
PR	1.78	(0.91-3.49)	0.091	1.62	(0.89-2.93)	0.112
Nodal status						
Negative	1.00			1.00		
Positive	2.25	(1.39-3.63)	0.001	2.02	(1.29-3.16)	0.002
Subtypes						
IDC	1.00			1.00		
LOB	1.58	(0.97-2.59)	0.069	1.50	(0.93-2.42)	0.099
TNBC						
No	1.00			1.00		
Yes	2.11	(1.45-3.08)	0.000	1.74	(1.20-2.53)	0.004
LVI						
No	1.00			1.00		
Yes	2.24	(1.49-3.37)	0.000	2.03	(1.36-3.02)	0.000

Table 3: Estimates of overall survival (OS) and distant relapse free survival (DRFS) and clinical parameters among patients

	OS			DRFS		
	Hazard Ratio	95% Confidence Interval	P value	Hazard Ratio	95% Confidence Interval	P value
Age group						
Age < 50	Reference			Reference		
Age >= 50	2.14	(1.22-3.75)	0.008	1.26	(0.79-2.00)	0.336
Pathological response						
CR	Reference			Reference		
NR	2.10	(0.67-6.64)	0.205	2.34	(0.81-6.73)	0.114
PR	1.21	(0.41-3.56)	0.733	1.25	(0.47-3.34)	0.661
Nodal status						
Negative	Reference			Reference		
Positive	1.97	(0.95-4.11)	0.068	1.63	(0.83-3.23)	0.159
TNBC						
No	Reference			Reference		
Yes	2.49	(1.53-4.04)	0.000	1.82	(1.13-2.93)	0.015
LVI						
No	Reference			Reference		
Yes	1.87	(1.14-3.07)	0.013	1.77	(1.10-2.84)	0.018

Table 4: Cox proportional hazards models for OS and DRFS among patients

Discussion

This series represents the largest collection of UK IBC cases published to date, and is the first to report the UK incidence of IBC. Our data indicates that IBC accounts for approximately 1% of invasive breast cancer cases in the UK suggesting that approximately 500 new cases of IBC are diagnosed in the UK each year [16]. Minor variations in incidence figures between participating breast cancer units (range 0.4%-1.8%) may reflect different local interpretations of diagnostic guidelines in the absence of unique histological identifiers and small absolute numbers involved. The figure of 1.0% is slightly lower than US series [2] and may reflect different population structures in the UK and US: young black and Hispanic women have an increased risk of IBC,

and the UK has a lower population percentage of these groups than the US [17]. Although our ethnicity data are not complete, 4.8 % of patients in this series of UK IBC cases were black, compared to 1.2% of all UK cases of invasive breast cancer reported in the 2011 National Cancer Intelligence Network report [6]. The Median age at diagnosis in this series was 56 years compared to 62 years for unselected UK invasive breast cancer cases (registry data) [6]. The US Breast Cancer Surveillance Consortium similarly reported lower age of onset of IBC compared to non-IBC or LABC patients (57.3 vs 60.7 years) [17]. The percentage of patients in this series who were obese at the time of presentation (41.3%) is higher than studies of non-inflammatory or unselected breast cancer (10.3-27.3%, reviewed by Renehan et al.[18]) and is supportive of epidemiological studies which indicate that obesity is a significant risk factor for IBC [17].

Almost one-fifth of patients received antibiotic therapy for presumed infection prior to attending the diagnostic breast clinic, highlighting frequent delays in diagnosis of IBC. The observation of a measurable mass on sonography in a high proportion of cases is consistent with other series and supports recommendations for ultrasound guided core biopsies as the primary diagnostic procedure [9,13]. Punch biopsies, which are also recommended in recent UK and US guidelines [9,13], were however performed rarely and changes in patient pathways will be required to support widespread adoption of this recommendation. As in most other reported IBC series, over 20% of patients had distant metastases at presentation justifying the UK IBC consortium recommendation to perform a staging CT scan at diagnosis [13].

Pathological profiles were very similar to those reported elsewhere with a higher proportion of ER negative tumours and HER2 positive tumours than found in non-IBC [12,17].

A high proportion of non-metastatic patients identified in our retrospective cohort received treatment with neo- adjuvant chemotherapy, surgery and radiotherapy (trimodality treatment) [19]. Randomised controlled trial evidence for the optimum chemotherapeutic regimen in IBC, is lacking. Previous retrospective series have reported improved pCR rates and overall survival with

taxanes [20]. The pCR rate in our cohort was 18.1% which compares well to other published series (15.2-18.0%) despite lower use of taxanes here [19,21]. Our data show a higher pCR rate in patients receiving taxanes; that this does not reach statistical significance for the overall cohort, or for triple negative patients (data not shown) may be due to small absolute numbers.

A small number of IBC patients with lobular histology show trend to worse overall survival when compared IDC patients. While most of the previous studies did not specifically compare survival data for IDC and ILC patients in IBC, a recent study by Raghav and colleagues found no differences between the groups in the 3-year overall survival rates [22]. Examination of larger IBC cohorts with carefully defined histological lobular carcinoma subtypes (e.g. the more aggressive pleomorphic type which has a less favourable outcome compared versus the classical lobular carcinoma) will be necessary to further clarify whether ILC-IBC behaves differently when compared to IDC-IBC.

Rates of pCR varied significantly according to biological subtype, with the highest pCR rate in HER2+ER- patients, as also reported by Masuda *et al.* [19]. As anticipated with >90% of patients recruited after 2005, there was high use of neo/adjuvant trastuzumab in this cohort; 86.0% of our stage 3 HER2 positive patients receiving this treatment compared to 35.6% of HER2 positive patients in the last UK IBC series [23]. In HER2 positive patients, trastuzumab use was associated with a higher pCR rate than chemotherapy without trastuzumab (27.5% vs. 14.3%); very small numbers in the no-trastuzumab group may explain why this does not reach statistical significance. The benefit of neo-adjuvant trastuzumab in IBC was confirmed by the NOAH clinical trial in which trastuzumab was associated with a hazard ratio for event-free survival of 0.27 in the IBC subgroup (n=63) [24]. Only 3 patients in our series received dual HER2 blockade; this may increase in the future given evidence from the NeoSPHERE and NeoALTO trials that pCR rates are enhanced by the addition of pertuzumab and lapatinib [25, 26].

Three patients received bevacizumab. Treatment with anti-angiogenic agents is a theoretically attractive proposition in IBC given the highly angiogenic nature of these tumours and the ARTEMIS trial, of anthracycline/taxane neo-adjuvant chemotherapy with or without bevacizumab, included a small number of IBC patients. However, exploratory analysis found no benefit from addition of the anti-angiogenic agent in the IBC group [27].

Most patients underwent mastectomy, however a small number had breast conserving surgery or skin-sparing mastectomies. Although US guidelines state that the only surgical procedure to be offered for IBC should be a modified radical mastectomy, the recent UK consensus acknowledges a paucity of data and suggests that “attempted breast conservation after adequate downstaging can be considered based on multidisciplinary review of pre- and post-treatment clinical, radiological and pathological features” [9,13]. Earlier data from the Royal Marsden Hospital have shown comparable OS rates for patients who did and did not undergo surgery [23], and Bonev *et al.* observed no difference in OS between IBC patients who underwent a modified radical mastectomy and those having partial mastectomy [28]. Similarly, in another study no statistically significant differences in breast cancer specific survival and OS were observed for patients treated with mastectomy or BCS [29]. A recent non-comparative single-centre series describes 35 IBC patients treated with BCS and reports locoregional recurrence in 5 cases but followed rapidly by distant metastases in 4 of these; the authors suggest that LRR in patients after BCT appears part of widespread recurrent disease rather than inadequate local treatment [30]. Analysis of patients in our cohort shows no significant difference in OS between patients treated with radical mastectomy, versus those having skin sparing or breast conserving surgery, but the number in the latter group is very small (n=20) and this result should be treated with caution (supplementary Figure 1). Our higher LR recurrence rate in mastectomy patients than BCS patients suggests confounding and is difficult to interpret given the amount of missing LR recurrence data in this cohort, and small number of BCS cases.

Despite use of trimodality treatment in 86.5% of stage III patients, outcomes were still poor with 40.1% of patients developing distant metastases and a 5-year OS of 61.0% with median survival of 7.5 years. The previous largest UK series describing 155 patients with IBC, treated at RMH between 1990 and 2007, reported median survival of 45 months in stage 3 patients [23]. Almost half of these patients were diagnosed before 1990 and there is significantly less use of anthracycline/ taxane chemotherapy in this cohort than in our series. Three contemporary US reports contain very similar results to ours (5-year OS of 51%-61%) in patients receiving trimodality treatment [12, 31, 32]. Poor outcomes were particularly seen in triple negative patients, with a recurrence rate of 56.7%, and a 5-year OS of only 37.7%, similar to the 39.0-42.7% OS observed elsewhere [12,21]. Patients who achieved a pCR had a significantly better 5-year OS than non-pathological CR patients, but still developed metastatic disease in 24% of cases.

The high incidence of brain metastases as a first site of metastatic disease in our IBC cohort (23%) is similar to that reported in a large American series [11]. Analyses in non-inflammatory breast cancer have identified the brain as first site of metastatic disease in <8.0% of cases [33,34]. Clinicians treating IBC patients should have a low threshold for suspecting CNS involvement in the event of neurological symptoms, particularly in patients with ER negative and/or HER2 positive disease.

Inevitably, this study is limited by its retrospective nature. All diagnoses of IBC were made locally, based on clinical features at the time of presentation. It is not possible to confirm definitively that all cases fulfilled all diagnostic criteria for IBC, and highlights the need to collect data prospectively, including clinical photographs and imaging data. Biases in patient selection may have arisen through the search mechanisms used at some hospitals; some breast units searched databases for patients treated with neo-adjuvant chemotherapy to find IBC cases and may have missed patients not treated with this modality. As with any retrospective review there is missing data; this is not entirely random but determined by availability of data sources which

varied significantly from hospital to hospital according to local archiving arrangements of paper and electronic patient records. In addition, some missing data points are the result of routine UK clinical practice during the earlier years of the study period, for example PR status was not routinely tested at many NHS hospitals for much of the study period as testing is not mandated by the UK National Institute of Clinical Excellence. However, for many variables there is less missing data here than in previous reports based on registry data. In particular, there is relatively little missing HER2 data here compared to series from the SEERS registry which has not routinely collected this [17].

Summary

IBC patients represent a small proportion of UK invasive breast cancer cases but have an aggressive clinical course with a poor outcome, particularly in patients with triple negative cancer and in the majority of patients who do not achieve a complete pathological response to neo-adjuvant chemotherapy. This study highlights the need for prospective data collection. A UK multi-centre prospective study, with biological sampling to facilitate translational research, is now in development.

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Conflict of Interest Statement:

EC has received honorarium from Roche and travel expenses from Astra-Zeneca.

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Ethical approval:

Formal ethical approval was not required for this study as it is a retrospective audit. All data collections, storage and transfer were registered as required by the individual institutions involved and were performed using fully anonymised data according to institutional governance protocols and as permitted by the NHS.

Authors' Contributions

E.C., F.B. provided intellectual input, conceptual framework, and designed the study. E.C, A.S., T.M., H.M., A.B., M.B., S.Y.T.C., R.I.C., I.D., B.D., A.L., I.M. P.M.M., D.R., E.S., N.S., L.J. D.M.E., and F.B. were each involved in drafting the manuscript, and took part in critically reviewing it for publication. EC, TM and HM performed the statistical-analysis. EC, FB, and DR analysed and interpreted the data. E.C, A.S., H.M., J. B, A.B., M.B., J.C., S.Y.T.C., C., I.D., B.D.,

M.K., A.L., I.M., P.M.M., D.R., L.R., V.R., E.S., N.S., T.S., L.J. D.M.E., and F.B. conducted collection and management of patient data.

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References

1. Lee BJ, Tannenbaum NE (1924) Inflammatory carcinoma of the breast: a report of twenty-eight cases from the breast clinic of the Memorial Hospital. *Surg Gynecol Obstet* 39:580-595.
2. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH (2005) Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. *J Natl Cancer Inst* 97:966-975.
3. Woodward WA (2015) Inflammatory breast cancer: unique biological and therapeutic considerations. *Lancet Oncol* 16:e568-e576.
4. Natori A, Hayashi N, Soejima K, Deshpande GA, Takahashi O, Cristofanilli M et al (2013) A comparison of epidemiology, biology, and prognosis of inflammatory breast cancer in Japanese and US populations. *Clin Breast Cancer* 13:460-464.
5. Ionta MT, Atzori F, Massidda B (2010) Inflammatory breast cancer in Italy: epidemiological and clinical aspects. *Cancer* 116(11 Suppl):2736-2740.
6. National Cancer Intelligence Network. The second all breast cancer report. 2011. <http://www.ncin.org.uk/view.aspx?rid=612>. Accessed March 2016
7. Haagensen CD (1956) Diseases of the female breast. *Trans N Engl Obstet Gynecol Soc* 10:141-156.
8. Edge SB, Byrd DR, Compton CC. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer;2010.
9. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA et al (2011) International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol* 22:515-523.
10. Bonnier P, Charpin C, Lejeune C, Romain S, Tubiana N, Beedassy B et al (1995) Inflammatory carcinomas of the breast: a clinical, pathological, or a clinical and pathological definition? *Int J Cancer* 62:382-385.
11. Matro JM, Li T, Cristofanilli M, Hughes ME, Ottesen RA, Weeks JC et al (2015) Inflammatory breast cancer management in the national comprehensive cancer network: the disease, recurrence pattern, and outcome. *Clin Breast Cancer* 15:1-7.
12. Rehman S, Reddy CA, Tendulkar RD (2012) Modern outcomes of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys* 84:619-624.
13. Rea D, Francis A, Hanby AM, Speirs V, Rakha E, Shaaban A et al (2015) Inflammatory breast cancer: time to standardise diagnosis assessment and management, and for the joining of forces to facilitate effective research. *Br J Cancer* 112:1613-1615.
14. Harvey JM, Clark GM, Osborne CK, Allred DC (1999) Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 17: 1474-1481.
15. Pinder SE, Provenzano E, Earl H, Ellis IO (2007) Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. *Histopathology* 50:409-417.
16. Cancer Research UK. Breast cancer incidence, UK. 2012. <http://info.cancerresearchuk.org/cancerstats/types/breast/incidence>. Accessed March 2016

17. Schairer C, Li Y, Frawley P, Graubard BI, Wellman RD, Buist DS et al (2013) Risk factors for inflammatory breast cancer and other invasive breast cancers. *J Natl Cancer Inst* 105:1373-1384.
18. Renehan AG, Harvie M, Cutress RI, Leitzmann M, Pischon T, Howell S, Howell A. (2016) How to manage the obese patient with cancer. *J Clin Oncol*. 34: 4284-4294.
19. Masuda H, Brewer TM, Liu DD, Iwamoto T, Shen Y, Hsu L et al (2014) Long-term treatment efficacy in primary inflammatory breast cancer by hormonal receptor- and HER2-defined subtypes. *Ann Oncol* 25:384-391.
20. Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, Kau SW, Frye DK, Hortobagyi GN (2004) Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: the M. D. Anderson Cancer Center experience. *Clin Breast Cancer* 4:415-419.
21. Li J, Gonzalez-Angulo AM, Allen PK, Yu TK, Woodward WA, Ueno NT et al (2011) Triple-negative subtype predicts poor overall survival and high locoregional relapse in inflammatory breast cancer. *Oncologist* 16:1675-1683.
22. Raghav K, French JT, Ueno NT, Lei X, Krishnamurthy S, Reuben JM et al (2016) Inflammatory Breast Cancer: A Distinct Clinicopathological Entity Transcending Histological Distinction. *PLoS One* 11:e0145534.
23. Sutherland S, Ashley S, Walsh G, Smith IE, Johnston SR (2010) Inflammatory breast cancer--The Royal Marsden Hospital experience: a review of 155 patients treated from 1990 to 2007. *Cancer* 116(11 Suppl):2815-2820.
24. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S et al (2010) Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*; 375:377-384.
25. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC et al (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*; 13:25-32.
26. de Azambuja E., Holmes AP, Piccart-Gebhart M, Holmes E, Di CS, Swaby RF et al (2014) Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 15:1137-1146.
27. Earl HM, Hiller L, Dunn JA, Blenkinsop C, Grybowicz L, Vallier AL et al (2015) Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. *Lancet Oncol* 16:656-666.
28. Bonev V, Evangelista M, Chen JH, Su MY, Lane K, Mehta R et al (2014) Long-term follow-up of breast-conserving therapy in patients with inflammatory breast cancer treated with neoadjuvant chemotherapy. *Am Surg* 80:940-943.
29. Chen H, Wu K, Wang M, Wang F, Zhang M and Zhang P (2017). A standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: A large population-based study in the Surveillance, Epidemiology, and End Results database 18. *The Breast* 35:48-54.
30. Brzezinska M, Williams, L.J., Thomas J and Dixon J.M (2016)..Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. *Breast Cancer Res Treat*

DOI 10.1007/s10549-016-4017-3

31. Bristol IJ, Woodward WA, Strom EA, Cristofanilli M, Domain D, Singletary SE et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys* 2008; **72**(2):474-484.
32. Damast S, Ho AY, Montgomery L, Fornier MN, Ishill N, Elkin E et al (2010) Locoregional outcomes of inflammatory breast cancer patients treated with standard fractionation radiation and daily skin bolus in the taxane era. *Int J Radiat Oncol Biol Phys* 77:1105-1112.
33. Berman AT, Thukral AD, Hwang WT, Solin LJ, Vapiwala N (2013) Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. *Clin Breast Cancer* 13:88-94.
34. Heitz F, Rochon J, Harter P, Lueck HJ, Fisseler-Eckhoff A, Barinoff J et al (2011) Cerebral metastases in metastatic breast cancer: disease-specific risk factors and survival. *Ann Oncol* 22:1571-1581.

Highlights

- The incidence and behaviour of inflammatory breast cancer (IBC) in the UK has not previously been studied beyond small single centre reviews
- We performed a multi-centre retrospective review of IBC cases from 14 UK and Irish hospitals
- IBC cases accounted for 0.4-1.8% of invasive breast cancer cases at these centres
- Despite trimodality (neoadjuvant chemotherapy/ surgery and radiotherapy) treatment in 86.4%, 40.1% of stage III patients developed distant metastases
- Five-year overall survival (OS) was 61.0% for patients with stage III disease at presentation